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LEVOPHED AND ARAMINE

In the absence of definitive studies, comparison of the overall effectiveness of different vasopressors in the relief of shock is difficult; but since choices must be made, it is hoped that the following discussion of two widely used agents, Levophed and Aramine, will be helpful. This discussion supplements the general review of vasopressors that appeared in The Medical Letter, March 18, 1960. (Comments on Wyamine, Vasoxyl, Neo-Synephrine and Methedrine will appear in a later issue.) The introductory sentences of the Medical Letter review bear reemphasis: "Acute arterial hypotension, or shock, is a symptom and not a disease, and wherever possible the underlying causes must, of course, be corrected. But when the causes are obscure or not immediately correctable, or when the duration of the shock is unpredictable (as in myocardial infarction...) the doctor may have to rely on vasopressor drugs to prevent irreversible tissue damage."

I. LEVOPHED - Norepinephrine (Levophed - Winthrop) is a vasopressor that has repeatedly proved its value in the clinical management of some types of acute hypotension, especially of myocardial infarction. Its blood-pressure elevating effect is due primarily to the peripheral vasoconstriction it induces, but it also has direct myocardial (inotropic) effects (D. M. Aviado, Jr., Anesthesiology, 20:71, 1959). Levophed is the bitartrate salt of l-norepinephrine, the substance released at post-ganglionic adrenergic nerve endings. It must be given by intravenous infusion, preferably through a polyethylene catheter to avoid extravasation and slough. Maximal effect is achieved with approximately 0.75 mcg./kg./minute (7 1/2 cc. per minute for an 80-kg. man, with a solution of 8 mg. of the base [two 4-cc. ampules] per liter); failure to respond to this amount calls for a search for causes of shock not amenable to vasopressors (blood loss, gastric perforation, or adrenal cortical insufficiency, for example).

DISADVANTAGES - The disadvantages of Levophed are: (1) constant supervision is needed to prevent dangerous fluctuation of blood pressure and to avoid slough from inadvertent extravasation outside the vein (when extravasation is detected in time, slough can be prevented by multiple injections into the entire affected area of a total of 10 mg. of phentolamine [Regitine] or 5 mg. of piperoxan [Benodaine] in 5 cc. of physiologic saline); (2) prolonged intravenous drip may require more fluid than is desirable, particularly in cardiac patients; (3) it can precipitate ventricular arrhythmia during or after certain types of general anesthesia; (4) loss of responsiveness to the drug may occur; (5) perhaps most important of

all, during Levophed-induced elevation of blood pressure, peripheral blood flow is decreased (except in the coronary circulation) as the result of intense vasoconstriction; with prolonged use this decrease may be important in its effects on cerebral and renal circulation; (6) blood pressure may fall after Levophed is stopped, possibly as a result of ganglionic blockade. Because of these disadvantages and in spite of the demonstrated effectiveness of Levophed in some cases of shock, the use of other vasopressors may be preferable.

II. ARAMINE - The specific advantages claimed for metaraminol (Aramine - Merck) are: (1) direct beneficial effect on myocardium in coronary shock (positive inotropic effect); (2) absence of sloughing or tissue necrosis following subcutaneous extravasation; (3) prolonged duration of action; (4) lack of need for a large volume of fluid; (5) less renal constriction with equal pressor response; (6) absence of tachyphylactic effect; (7) pressor effect in one to two minutes after intravenous injection.

Although slough has been reported after extravasation of intravenous Aramine (W. E. Dippy and E. R. Dorney, JAMA, 170:1647, 1959; R. O. Shaub, JAMA, 172:154, 1960), the causal connection between the extravasation and the slough has been questioned. Intramuscular and subcutaneous injections have been well tolerated. For the most part, the claims appear to represent real advantages over Levophed. Experimentally, Aramine has been shown to predispose to induced ventricular arrhythmias, but this effect does not appear to be clinically significant. To be safe, however, Aramine should not be given with cyclopropane.

ADMINISTRATION - Aramine may be given subcutaneously, intramuscularly or intravenously. When speed is demanded it may be given intravenously without dilution, to be followed by slow intravenous infusion or a series of subcutaneous or intramuscular injections. Since pressor effects are evident within two minutes and reach a peak about five minutes after intravenous injection, it is probably wisest to start with no more than 1 or 2 mg., repeating this dosage after five to 10 minutes if necessary. If the subcutaneous or intramuscular route is used to start treatment, maximum effect is probably not reached for about 30 minutes. The duration of effect is 10 to 30 minutes after intravenous injection, several times as long after intramuscular injection, and longer still after subcutaneous injection.

Blood pressure is best maintained by subcutaneous or intramuscular injections of 2 to 10 mg. whenever it falls below the desired level. It will generally be found that the larger amount can be used safely at half-hour to two-hour intervals. Decreasing the dosage is usually preferable to decreasing the frequency of injections as the need for pressor effect gradually lessens. If maintenance of pressor effect by intravenous infusion is preferred, 15 to 100 mg. per 500 cc. of diluent may be used.

Unlike Levophed, Aramine can be given with relative safety at home, prior to hospitalization, or in the absence of constant attendance in the hospital. Final evaluation of Aramine will require more extensive clinical trial than it has had thus far, but at this point there is little doubt that it is a valuable agent for the management of shock.

PRELUDIN

Phenmetrazine (Preludin - Geigy) is a sympathomimetic-amine appetite depressant pharmacologically similar to the amphetamines. Its effect on appetite appears to be about the same as that of dextroamphetamine. The claim is made, however, that unlike the amphetamines, Preludin "curtails appetite and improves mood of dieting patients without producing jitteriness, nervous tension or disturbance of sleep."

SIDE EFFECTS - E. P. Gelvin, et al. (Am. J. Digest. Dis., 1:155, 1956) found the incidence of side effects with Preludin little greater than with a placebo; J. F. Fazekas, et al. (Am. J. Med. Sci., 236:692, 1958) found the side effects of the drug and of a placebo comparable; and R. H. Barnes (JAMA, 166:898, 1958) reported that relatively larger doses of Preludin can be given "without the untoward side-effects of nervousness, cardiac palpitation, headache, dry mouth, and restlessness noted in large dosages of amphetamine products."

On the other hand, P. Szenas and C. J. Patee (Can. Serv. Med. J., 13:195, 1957) found a 48 per cent incidence of side effects with Preludin and 60 per cent with amphetamine. Another study (M. Patterson, Antib. Med. & Clin. Ther., 6:207, 1959) noted a 40 per cent incidence of side effects with Preludin as against 17 per cent with dextroamphetamine, a difference, however, which is declared to be "not statistically significant." And J. B. Randell (Brit. Med. J., 2:508, 1957), after a study of the effects of Preludin on 10 normal student volunteers, reported that single daily doses of 25 mg. and 50 mg. produced palpitation, insomnia, perspiration, restlessness, irritability, and difficulty of concentration (the recommended dosage is 25 mg. two or three times daily).

All of these citations on side effects are given because the main question about this drug is whether it is relatively free of unwanted effects (the manufacturer does not claim that its anorexigenic effects are greater than those of dextroamphetamine). Unfortunately, large-scale, carefully-controlled, double-blind trials directly comparing the side effects of the two drugs are lacking. Medical Letter consultants see no basis in present evidence for a choice between the two in terms of either appetite-depressing effects or side effects.

Both drugs have a euphoriant effect which is sometimes desirable in helping the patient through the difficult period of adjustment to a low-calorie diet, but tolerance develops with both drugs, and overdosage and addiction can be a problem. Addiction to Preludin has often been reported in Britain where, until recently, the drug was available without prescription (J. Evans, Lancet, 2:152, 1959). Overdoses of any sympathomimetic-amine including Preludin can, of course, produce nervousness, sleeplessness, and toxic psychosis.

DOSAGE - Preludin is available in 25-mg. tablets (equivalent to 5 mg. of dextroamphetamine), which are usually taken one-half to one hour before meals. Preludin Endurets, a sustained-release preparation containing 75 mg., are taken once daily, before breakfast. The same limitations arising from unpredictability of absorption apply to Endurets as to long-acting dextroamphetamine preparations (The Medical Letter, 2:11, Feb. 5, 1960).

In summary, Preludin, like dextroamphetamine, does tend to depress appetite and to make it easier for some obese patients to limit food intake - at least temporarily. Both agents tend to lose their effectiveness with prolonged use. For the long term, the doctor must rely on carefully controlled diet, moderate exercise and psychotherapy, rather than on drugs, in treating the obese patient. Preludin tablets, when purchased in quantities of a hundred, cost the patient about 8¢ apiece, as compared with 5¢ or 6¢ for 5-mg. tablets of Dexedrine (SKF) and about 3¢ for 5-mg. tablets of lower-priced brands of dextroamphetamine sulfate, sold under its generic name.

HOMAGENETS AND VITAMIN ABSORPTION

Homagenets (Massengill) are offered as "the only homogenized vitamins in solid form." By means of a homogenization process, it is claimed, both oil- and water-soluble vitamins are made available in microscopic particles, permitting quicker absorption and better utilization. Various mixtures of vitamins and of vitamins and minerals, ranging from "prenatal" to "geriatric," are offered in a variety of Homagenet preparations, all in "candy" form.

The only published reference cited in support of the claims for Homagenets is a report by J. M. Lewis, et al. (J. Pediat., 31:496, 1947). At the time of this study there was no such product as Homagenets. Lewis and his co-workers showed only that an oral dose of an aqueous dispersion of vitamin A (as contained in Vi-Penta - Roche) gave higher blood levels of the vitamin in both children and adults than did an equal dose of vitamin A in an oily solution. None of the other vitamins contained in Homagenets were included in the study.

VITAMIN A ABSORPTION - It is now generally accepted that vitamin A is absorbed more rapidly and more completely from aqueous than from oily media, but it is difficult to see the connection between this fact and the claims for Homagenets, particularly in view of a later report (J. M. Lewis, et al., Pediatrics, 5:425, 1950) showing that the microscopic particles in emulsified, or homogenized, preparations of vitamin A are not so well absorbed as the submicroscopic particles in aqueous preparations.

Even if vitamin A is better absorbed from Homagenets than from oily preparations, the difference would have little clinical significance, since most patients have no absorption difficulties and since, in the prevention and treatment of vitamin deficiencies, adequate tissue levels of vitamin A and other vitamins are achieved by conventional vitamin products (tablets, capsules, drops, etc.). In cystic fibrosis of the pancreas and other disorders of fat absorption, adequate absorption of fat-soluble vitamins is obtained with aqueous dispersions (A. E. Sobel, Vitamins and Hormones, Vol. X, p. 47, 1952).

The only apparent advantage of Homagenets - the candy form - is offset by the temptation offered the child to take much more than he should. Though Homagenets cost more than many competitively-priced vitamin preparations, they are comparable in price to other "name" brands. The "therapeutic" Homagenet tablets cost the patient about 8¢ apiece, the "pediatric" Homagenets, about 6¢.

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